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Review

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ABSTRACT

Immunoglobulin A vasculitis (IgAV), also referred to as Henoch-Schönlein purpura, is the most common form of childhood vasculitis. The pathogenesis of IgAV is still largely unknown. The disease is characterized by IgA1-immune deposits, complement factors and neutrophil infiltration, which is accompanied with vascular inflammation. Incidence of IgAV is twice as high during fall and winter, suggesting an environmental trigger associated to climate. Symptoms can resolve without intervention, but some patients develop glomerulonephritis with features similar to IgA nephropathy that include hematuria, proteinuria and IgA deposition in the glomerulus. Ultimately, this can lead to end-stage renal disease. In IgA nephropathy immune complexes containing galactose-deficient (Gd-)IgA1 are found and thought to play a role in pathogenesis. Although Gd-IgA1 complexes are also present in patients with IgAV with nephritis, their role in IgAV is disputed. Alternatively, it has been proposed that in IgAV IgA1 antibodies are generated against endothelial cells. We anticipate that such IgA complexes can activate neutrophils via the IgA Fc receptor FcαRI (CD89), thereby inducing neutrophil migration and activation, which ultimately causes tissue damage in IgAV. In this Review, we discuss the putative role of IgA, IgA receptors, neutrophils and other factors such as infections, genetics and the complement system in the pathogenesis of IgA vasculitis.

Contents

1. Introduction . . . 1247
2. IgA and IgA receptors . . . 1247
3. The role of galactose-deficient IgA1 in IgA vasculitis . . . 1248
   3.1. Galactose-deficient IgA1 and immune complexes . . . 1248
   3.2. Mesangial deposition of Gd-IgA1-immune complexes in IgAVN . . . 1248
   3.3. The presence of Gd-IgA1 in IgA vasculitis . . . 1249
4. The role of anti-endothelial cell antibodies in IgA vasculitis . . . 1249
5. Additional factors involved in IgAV . . . 1249
   5.1. The involvement of complement . . . 1249

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AECA, Anti-epithelial cell antibodies; ANCA, Anti-neutrophil cytoplasmic antibodies; β2GPI, β2-glycoprotein I; CDC, Complement-dependent cytotoxicity; EC, endothelial cell; FcαRI, Fc receptor for IgA; GalNAc, N-Acetylgalactosamine; Gd-IgA1, Galactose deficient immunoglobulin A1; IgA, immunoglobulin A; IgAN, Immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; IgAVN, Immunoglobulin A vasculitis with nephritis; ITAM, Immunoreceptor Tyrosine-based Activation Motif; ITAMi, Inhibitory Immunoreceptor Tyrosine-based Activation Motif; LABD, linear IgA bullous disease; NETs, neutrophil extracellular traps; pIgR, Polymeric Immunoglobulin receptor; RA, Rheumatoid arthritis; ROS, reactive oxygen species; sCD89, Soluble CD89 (Fc alpha receptor); SIgA, secretory IgA; TFR, transferrin receptor; TG2, transglutaminase 2.

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5.2. Genetics . . . 1250
5.3. Infections . . . 1250
6. Two models to explain pathogenesis of vasculitis and glomerulonephritis . . . 1250
6.1. Multi-hit model for glomerulonephritis in IgAN and IgAVN . . . 1250
6.2. Multi-hit model for vasculitis in IgAV and IgAVN . . . 1250
7. Open questions and future research . . . 1251
8. Conclusion . . . 1251
Disclosure of conflict of interest . . . 1251
Acknowledgements . . . 1251
References . . . 1252

1. Introduction

IgA vasculitis (IgAV), also referred to as Henoch-Schönlein purpura, is characterized by immunoglobulin A1 (IgA1)-dominant immune deposits affecting small vessels, and often involves skin, gastrointestinal tract, joints, and kidney [1]. IgAV is the most common form of childhood vasculitis with a reported annual incidence rate of 3–26,7/100.000 [2,3], although it is likely that the incidence is underestimated due to underreporting. Ten percent of the total patient population is adult, with an annual incidence rate of 0,8–1,8/100.000 [2]. A higher incidence of IgAV is reported in both adolescent and adult males than females [3]. The disease is most prevalent in South-East Asia and to a lesser extent in Europe and North-America, but IgAV is rare in Africa [2,4]. Symptoms include palpable purpura or petechiae, (poly)arthralgia, gastrointestinal disturbances and glomerulonephritis (Table 1). Cutaneous hemorrhages are a prerequisite for diagnosis and are caused by leakage of red blood cells into the skin or mucous membranes, possibly by a necrotizing vasculitis of small vessels in the dermis. Usually, the symptoms in the acute stage of disease are self-limiting and resolve without intervention. However, in part of the patients glomerulonephritis develops, which can lead to end-stage renal disease in a small percentage of pediatric patients.

Despite the fact that IgAV has been recognized for over 200 years and is the most common form of vasculitis, the causal pathogenic mechanisms have yet to be resolved. It is important to understand the causality, as this may lead to prevention of disease or to development of new therapeutics. Vascular inflammation is accompanied by IgA1 deposits, complement factors and large neutrophil infiltrates. IgA vasculitis with nephritis (IgAVN) resembles IgA nephropathy (IgAN). Both diseases are characterized by hematuria, proteinuria and immune complex deposition in the glomerular mesangium. However, IgA nephropathy is restricted to the kidneys, and it has been hypothesized that IgAV and IgAVN may represent systemic equivalents of IgAN [5]. Therefore, it is interesting to explore if pathogenic mechanisms proposed for IgAN may also apply for IgAV.

IgA is the main component of the immune deposits in IgA vasculitis. Its origin and specific target antigen(s) are unknown. Additionally, it is unclear why IgA complexes are deposited in the vasculature. In the next sections, several findings regarding the role of IgA in IgA vasculitis are highlighted, which are summarized in a multi-hit model to explain the pathogeneses of IgAV and IgAVN. This model differs from the multi-hit model which describes the pathomechanisms leading to glomerulonephritis during IgAVN and IgAN. Furthermore, we anticipate that IgA antibodies activate neutrophils via the IgA receptor FcαRI, thereby inducing neutrophil migration and activation, with concomitant tissue damage.

2. IgA and IgA receptors

Immunoglobulin A is a member of the human immunoglobulin family. It consists of two heavy and two light chains, with Fab regions that bind antigens and a Fc-tail which can interact with Fc receptors. IgA is mostly known as the dominant antibody subclass present in mucosal areas, where it plays a key role in mucosal defense. Mucosal secretory IgA (SIgA) provides 'immune exclusion' by binding to pathogens in a hydrophilic shell conformation, which is repelled from mucosal surfaces. Additionally, IgA can also neutralize bacterial products, agglutinate microbes and interfere with bacterial motility [6]. In the blood circulation, 1–3 mg/ml IgA is present as a monomeric molecule (mIgA or serum IgA) [7]. Two isoforms of IgA exist. Within the circulation approximately 90% of the IgA present is IgA1, whereas <10% is IgA2 [8]. IgA1 has an extended hinge region due to an insertion of two octapeptide repeats. The repeats have 3 to 6 common *O*-glycan sites to which *O*-glycans can be attached during glycosylation.

It has been shown that IgA can activate complement proteins. Complement is present in its inactive form in the circulation, and three pathways can lead to the activation of complement. IgA cannot activate the classical route of complement, since it is lacking a C1q binding site. However, it has been demonstrated that IgA can induce the mannan-binding lectin and alternative complement pathways [9,10]. Furthermore, IgA can bind to and activate multiple receptors. One of these is the transferrin receptor (CD71), which is universally expressed as a transmembrane glycoprotein. The transferrin receptor is important for the import of iron in the cell by binding to transferrin-iron complexes. It is thought that overexpression of this receptor by mesangial cells facilitates the deposition of IgA1-containing immune complexes in the mesangium (see also Section 3.1) [11]. The prototypic IgA receptor is FcαRI, which can be present as a transmembrane receptor on myeloid cells and in soluble form (sCD89). The soluble form is generated by shedding of the extracellular part of FcαRI from the membrane. Soluble FcαRI can form immune complexes with IgA and is thought to play a role in IgA nephropathy progression (see also Section 3.1) [12]. FcαRI is present as transmembrane receptor on several myeloid cell types and can act as bi-functional receptor. It is able to induce pro-inflammatory reactions but can also trigger inhibitory signals, a property that can be exploited to reduce the susceptibility to autoimmune and

Table 1
Overview of symptoms associated with pediatric IgAV [3].

Symptoms	Affected body area	Average duration	Estimated % of patients affected
Palpable purpura or petechiae	Skin (mainly lower extremities and lower parts of the arm)	3–10 days	100
(Poly)arthralgia	Joints (knees and ankles)	7–10 days	>80
Gastrointestinal disturbances (incl. hematochezia and colicky abdominal pain)	Lower digestive tract	4–8 days	>50
Glomerulonephritis	Kidney	3–12 days	40–50

inflammatory diseases [6]. FcαRI forms complexes with the FcR γ-chain, which contains Immunoreceptor Tyrosine-based Activation Motif (ITAMs) to propagate downstream signals. Monomeric IgA can bind to, but not cross-link FcαRI, inducing anti-inflammatory responses. Monovalent targeting of FcαRI results in the formation of intracellular structions named 'inhibisomes', which hamper signaling of neighboring activated receptors (like Fc epsilon receptors, Fc gamma receptors or Toll-like receptors) [13]. This process is termed inhibitory ITAM (ITAMi) signaling and results in the downregulation of immune activation [14,15]. In contrast, binding of IgA immune complexes to FcαRI on neutrophils induces activating ITAM signaling. Cross-linking of FcαRI results in multiple pro-inflammatory functions, such as phagocytosis, production of reactive oxygen species (ROS), release of granules containing toxic molecules such as lactoferrin, cytokine and chemokine secretion, antibody-dependent cellular cytotoxicity (ADCC) and the release of neutrophil extracellular traps (NETs) [16,17]. Furthermore, FcαRI triggering induces the release of chemoattractant LTB4, resulting in neutrophil migration [18].

The interaction between IgA and FcαRI has been implicated in several IgA mediated autoimmune diseases, such as linear IgA bullous disease (LABD), rheumatoid arthritis (RA) and ulcerative colitis [6,19,20]. These diseases are characterized by IgA autoantibodies which target self-antigens such as collagen XVII in LABD and the Fc domain of human IgG in RA. Since IgA autoantibodies can form complexes and activate neutrophils via FcαRI, this leads to pro-inflammatory effector functions, neutrophil recruitment and eventually to tissue destruction. Blocking the interaction between IgA and FcαRI was shown to reduce tissue damage in an ex vivo model of LABD [20]. Since both neutrophils and IgA are present in IgA vasculitis lesions, it is likely that the interaction between IgA and FcαRI plays a role in the pathogenesis of IgA vasculitis.

3. The role of galactose-deficient IgA1 in IgA vasculitis

3.1. Galactose-deficient IgA1 and immune complexes

In IgAN and IgAVN it has been shown that *O*-glycans in the hinge region of human IgA1 are aberrantly glycosylated [21,22]. Glycosylation is a post-translational modification which involves the addition of glycans, thereby influencing structure, form and effector functions of immunoglobulins [23]. It is hypothesized that genetic predisposition and/or mucosal infection and concomitant interleukin (IL)-6 production cause aberrant glycosylation by altering the glycosylation machinery [24]. IgA1 in IgAN and IgAVN is galactose-deficient (Gd-IgA1), thereby exposing subjacent GalNAc-residues, which can function as neoepitopes [21,22]. Autoantibodies recognizing GalNAc-structures can consequently form immune complexes by binding to Gd-IgA1 [25–29] (Fig. 1). The origin of these autoantibodies is poorly understood. Possibly, Gd-IgA1 itself induces production of anti-Gd-IgA1 autoantibodies, but they can also be cross-reactive antibodies which are previously produced in response to GalNAc-containing molecules on pathogens [30,31].

Additionally, it was shown that Gd-IgA1 forms complexes with soluble IgA Fc alpha receptor (sCD89) [32,33] (Fig. 1). This molecule can be shedded from the membrane of monocytes after activation of FcαRI [12]. sCD89 entails the extracellular part of the receptor, and is therefore capable of binding IgA. Serum levels of Gd-IgA1-sCD89 complexes in IgAN patients were found to correlate with disease severity and progression, but not with disease susceptibility [34]. Additionally, components in food may contribute to the pathogenesis of IgAN. Gliadin, a component of gluten, was shown to directly interact with sCD89, thereby aggravating IgAN development in a mouse model of IgAN [35]. A gluten-free diet may thus be beneficial for patients with IgAN.

3.2. Mesangial deposition of Gd-IgA1-immune complexes in IgAVN

In IgAVN, Gd-IgA1, autoantibodies and sCD89 form large immune complexes. Small circulating immune complexes are generally cleared by hepatocytes in the liver, but it is thought that large immune complexes cannot enter the liver via the Disse space [5,36,37]. This results in enhanced levels of circulating Gd-IgA1 immune complexes and eventual deposition of immune complexes in the glomerulus. Several molecules have been suggested to facilitate binding of Gd-IgA1 immune complexes to mesangial cells, including extracellular matrix proteins, integrins and the transferrin receptor CD71 [11,38,39]. In mice, it was shown that immune complexes containing Gd-IgA1 can bind to transferrin receptors on mesangial cells (Fig. 2). Subsequently, transglutaminase 2 (TG2) expression is induced on the mesangial cell surface, leading to upregulation of transferrin receptor expression [11,33,40]. Thus, initial binding of immune complexes to mesangial cells results in a positive feedback loop, resulting in enhanced immune complex deposition. Additionally, these complexes can activate mesangial cells to produce several cytokines, thereby affecting the glycosylation machinery and possibly enhancing the formation of Gd-IgA1 [40]. Gd-IgA1 containing immune complexes from IgAN patients were shown to stimulate mesangial proliferation and induce production of cytokines and components of the extracellular matrix. Interestingly, Gd-IgA1 alone does not have these stimulatory effects, thereby highlighting the crucial role of immune complexes for the induction of nephritis [36,41–46]. Additionally, the amount of circulating immune complexes was found to correlate with disease severity and progression [25,47,48]. Patients with IgAVN have an increased expression of transferrin receptors on their mesangium [49]. Furthermore, IgG present in immune complexes may bind to Fc gamma receptors on mesangial cells [50]. In summary, increased levels of Gd-IgA1-sCD89 complexes, together with the presence of Gd-IgA1-specific autoantibodies and local

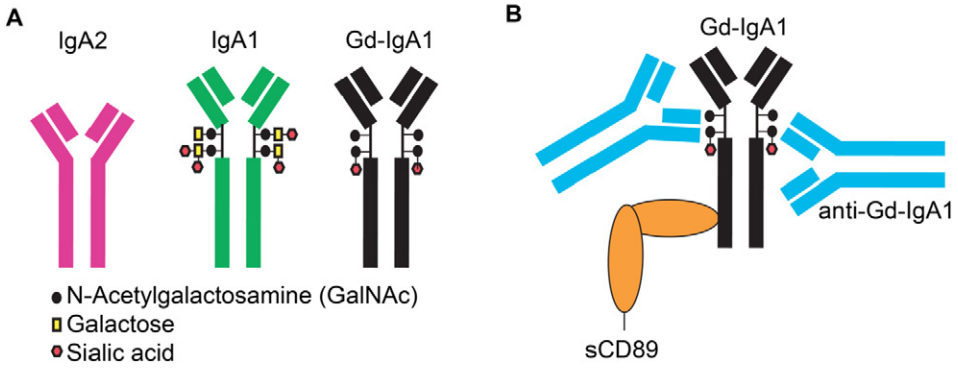

Fig. 1. Galactose-deficient IgA in immune complexes. (A) IgA2 does not have a hinge region, whereas the hinge region of IgA1 can be glycosylated. Healthy IgA1 is glycosylated with GalNAc (circle), galactose (square) and sialic acid (polygon). Galactose-deficient IgA1 does not contain galactose in its hinge region. (B) Gd-IgA1 can form immune complexes with IgG anti-Gd-IgA1 and soluble Fc alpha receptor (sCD89).

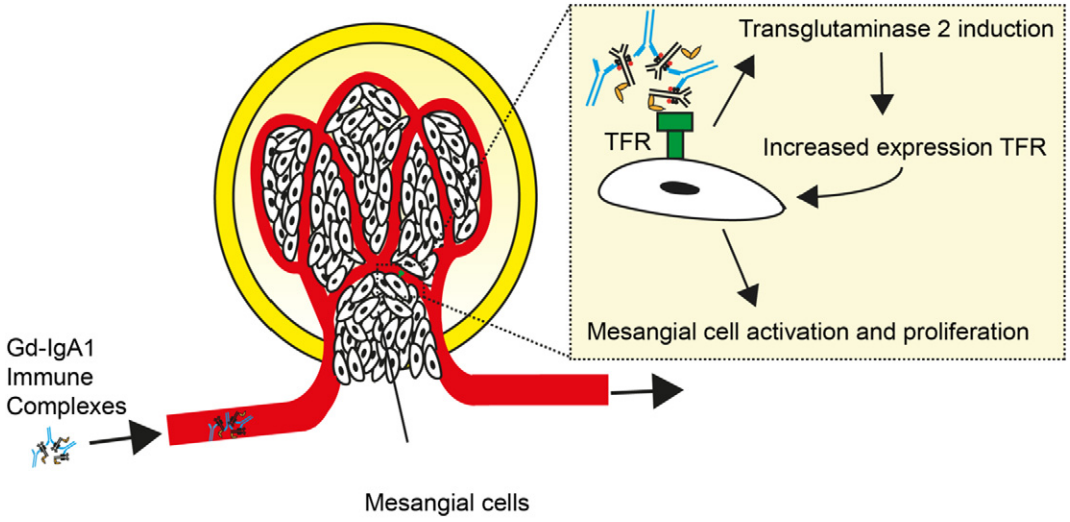

Fig. 2. The role of Gd-IgA1 in glomerulonephritis. Gd-IgA1 containing immune complexes are formed and circulate in the blood stream (see also Fig. 1). In the kidney, they bind to Transferrin Receptors (TFR) on mesangial cells. This induces expression of Transglutaminase 2, which leads to increased expression of TFR. Furthermore, binding of immune complexes induces mesangial cell activation, leading to production of cytokines, extracellular matrix components and proliferation.

activation of complement, may lead to inflammation of the glomerulus and impaired renal function [51].

3.3. The presence of Gd-IgA1 in IgA vasculitis

Although it is generally accepted that Gd-IgA1 plays a role in pathogenesis of IgAN and IgAVN, its presence and role in IgA vasculitis remain controversial. Two studies claim the absence of these molecules in IgAV patients, and found no differences in serum Gd-IgA1 levels between IgAV patients and healthy controls [28,29]. Additionally, immune complexes in sera of patients with IgAV did not contain IgG, whereas IgG immune complexes were found in IgAVN patients [52]. Possibly, the presence of IgG in immune complexes facilitates deposition on the glomerular mesangium. In conclusion, although immune complexes containing Gd-IgA1 are implicated in glomerulonephritis during IgAN and IgAVN, it is unknown if Gd-IgA1 plays a role in the pathogenesis of systemic inflammation during IgA vasculitis.

4. The role of anti-endothelial cell antibodies in IgA vasculitis

IgA vasculitis is characterized by IgA1-autoantibodies, but the (auto)antigen to which IgA1 binds is unknown. In several other vascular disorders, including systemic lupus erythematosus and systemic vasculitis, anti-endothelial cell antibodies (AECA) have been associated with disease [53]. AECA are a heterogeneous group of antibodies directed against poorly characterized antigens on human endothelial cells. IgA from serum of IgAV patients has been found to bind to human endothelial cells in vitro, supporting the presence of IgA

AECA [54]. It has been hypothesized that microorganisms have similar antigenic structures as human vessel walls. Infection with these microorganisms could lead to the production of cross-reactive AECA, although no specific microorganism has been identified in IgAV yet [54]. A possible candidate antigen is β2-glycoprotein I (β2GPI), as IgA from IgAV patients bound more avidly to this specific antigen than control IgA [55]. β2GPI is a serum molecule that binds to phospholipids on the endothelial cell surface [56]. Possibly, β2GPI adheres to endothelial cells and exposes antigens which are normally hidden [55]. Other autoantibodies recognizing β2GPI-associated phospholipids have been previously detected in serum of IgAV patients [57–60]. Interestingly, IgA AECA from IgAVN patients bound to bovine glomerular endothelial cells, whereas no binding of serum from IgAV patients was detected [61]. This suggests that antigen-specificity of AECA between IgAV and IgAVN patients may differ.

It is unclear which role AECA play in pathogenesis. AECA promoted vascular damage in several animal models by endothelial cell activation and ADCC or complement dependent cytotoxity (CDC) [62]. It was furthermore shown in vitro that IgA AECA from IgAV patients induced endothelial cells to produce cytokines such as IL-8, thereby promoting an inflammatory milieu and inducing neutrophil chemotaxis [63,64]. Elevated levels of systemic TNF-α during IgAV [65] might increase inflammation, as TNF-α enhanced binding of AECA to endothelial cells and induced IL-8 release by endothelial cells [54,64]. Furthermore, IgA AECA from IgAV patients induced CDC of endothelial cells in vitro [55]. It is unknown via which route complement was activated in these experiments. Additionally, in accordance with Yang et al. [54], we hypothesize that IgA induces neutrophil activation via FcαRI, resulting in neutrophil activation and chemotaxis (Fig. 3). Vascular damage is induced by IgA via inflammatory processes including ADCC, ROS production and NET formation. Additionally, IgA stimulation of neutrophils leads to the release of LTB4, inducing subsequent neutrophil migration in a positive feedback loop [18]. We have observed that FcαRI contributes to tissue damage in several IgA-mediated diseases, including LABD and RA [19,20]. Furthermore, in a tumor model, neutrophil targeting with IgA antibodies led to TNF-α release, which prompted endothelial cells to produce IL-8 and thereby enhanced neutrophil migration [66]. In conclusion, anti-endothelial cell antibodies might bind to autoantigens on endothelial cells, inducing cross-talk between IgA, neutrophils and endothelial cells, ultimately leading to neutrophil infiltration and vascular damage.

5. Additional factors involved in IgAV

5.1. The involvement of complement

The complement system is part of the innate immune system which can enhance attack or clearance of microbes. Skin and mesangial deposits in IgAV and IgAVN contain the complement components C3 and C5-C9 [5,67]. These components are able to form the membrane attack complex, which is capable of disrupting the membrane of target cells. Additionally, C5a is a neutrophil chemoattractant, which possibly enhances neutrophil recruitment during systemic inflammation. Furthermore, C3a and C5a increase the secretion of IL-8 by endothelial cells in vitro [67], thereby further attracting neutrophils. Involvement of the classical route of activation in IgAV is not likely, since IgA cannot activate the classical pathway and the main classical pathway activator C1q is not present in immune complexes. Several findings imply the

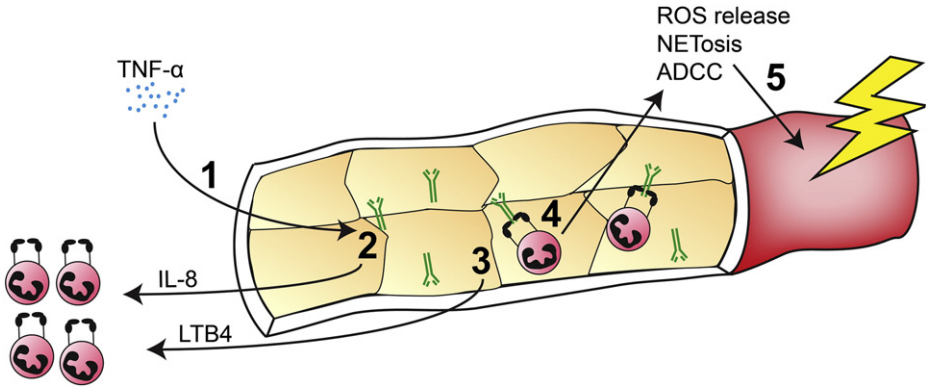

Fig. 3. The hypothesized role of AECA in IgA vasculitis. (1) TNF-α enhances binding of IgA1 AECA to endothelial cells. (2) Endothelial cells produce IL-8, inducing neutrophil migration. (3) The interaction between IgA1 AECA and FcαRI on neutrophils induces LTB4 release, inducing neutrophil recruitment. (4) Furthermore, the interaction of IgA and FcαRI induces release of ROS, NETosis and ADCC. (5) This ultimately leads to vascular damage.

alternative pathway of complement activation in IgAV etiology. Analysis of serum of acute pediatric IgAV patients showed a significant increase in levels of C3a, C5a and Bb but not of C4a [67]. Bb is the catalytic subunit of factor B, which is only involved in the alternative pathway. Furthermore, deletions in genes encoding for proteins that compete with complement factor H, a factor negatively regulating complement in the alternative pathway, were correlated with decreased susceptibility to IgAVN and IgAN [68,69]. Recently, the lectin binding pathway of complement activation has been implicated in IgAVN and IgAN as well, since IgA can activate mannan-binding lectin [9]. Additionally, factors involved in the lectin binding pathway have been found in glomerular depositions and serum of IgAN and IgAVN patients [70–72]. Complement was essential for the development of glomerulonephritis in an IgAN mouse model [73], but the exact pathomechanisms in IgAVN and IgAV require further investigation.

5.2. Genetics

Although no mutations have been shown to directly cause IgAV, several factors implicate genetic factors in pathogenesis of IgAV. First, IgAV incidence differs between ethnic groups, with highest incidence in South-East Asians and low incidence in African people [2]. In a study performed in England, African American children were four times less likely to develop IgAV, compared to children from Caucasian and Indian ancestry [4]. Second, although familial aggregation of IgAV is rare, several cases have been reported [74]. When comparing genetic variants between healthy and IgAV patients, the biggest difference was found in HLA genes. Variants HLA-DRB1*01 and HLA-DRB1*11 were associated with IgAV, whereas HLA-DRB1*07 was negatively associated with IgAV [75]. Irrespective of HLA-DRB1 status, HLA-B*41:02 was found to be a susceptibility marker for IgAV development [76]. HLA genes code for MHC molecules, which are important for antigen presentation to T cells. The involvement of HLA genes could indicate that antigen presentation and T cell activation are important in controlling autoimmune diseases [77]. Other genes involved in cytokine and chemokine production, the renin-angiotensin system, complement activation, and endothelium activity regulation have also been implicated in IgAV susceptibility [78–80].

5.3. Infections

Since IgA vasculitis regularly appears after bacterial or viral infections during the fall season, it is hypothesized that infections play a role in the etiology of IgAV. Possibly, GalNAc on the surface of pathogens may facilitate the production of cross-reactive IgA and IgG, which recognize Gd-IgA1 [30]. Alternatively, microorganisms could harbor antigenic structures resembling those of vessel walls, inducing the development of cross-reactive autoantibodies [54]. Additionally, mucosal infection leads to upregulation of IL-6, which could lead to development of Gd-IgA1 by altering the glycosylation machinery [24]. There is no particular infectious pathogen known to cause IgAV, although *Helicobacter pylori* has been associated with disease. IgAV patients with *H. pylori* infection improved after pathogen eradication, while recurrence of disease was associated with *H. pylori* recolonization [81]. Additionally, *H. pylori*-positive children had a 3.8 times higher chance to develop IgAV compared to uninfected children [82]. Interestingly, *H. pylori*-specific antibodies bound to affected renal tissue of IgAVN patients, possibly by binding to immune complexes or to renal tissue directly [83]. Furthermore, a virulence factor of *H. pylori* was shown to promote the production of Gd-IgA1, as it downregulated enzymes involved in galactosylation [84]. Other possible pathogenic microorganisms have been extensively reviewed in [78]. Interestingly, several bacteria, including *S. pneumonia* and *H. influenza*, secrete IgA1 proteases, which are capable of cleaving the hinge of IgA1 [85]. IgA1 proteases could also cleave Gd-IgA1, implying that these molecules could be used as therapeutic tool for IgA1-mediated diseases [86]. Indeed, it was shown that IgA1 proteases could be used to treat or prevent IgAN in vitro and in vivo [86–88].

6. Two models to explain pathogenesis of vasculitis and glomerulonephritis

6.1. Multi-hit model for glomerulonephritis in IgAN and IgAVN

Recently a multi-hit hypothesis for IgA nephropathy has been proposed by Novak et al. [22,36]. The first hit comprises the increased level of circulating Gd-IgA1, influenced by both environmental and genetic factors (Fig. 4A). Second, antibodies recognizing Gd-IgA1 are produced or already present, possibly attributable to molecular mimicry. The formation of Gd-IgA1-containing immune complexes is thirdly mediated by complement factors and IgA receptors such as CD71 and sCD89. Fourth, Gd-IgA1-containing immune complexes deposit in the mesangium, hereby inducing activation of human mesangial cells, which ultimately leads to renal dysfunction [22,36]. Although the model explains the renal symptoms as described for IgAN and IgAVN, it is unclear if Gd-IgA1 antibodies also play a role in the development of IgAV.

6.2. Multi-hit model for vasculitis in IgAV and IgAVN

Alternatively, we propose a multi-hit hypothesis to explain the systemic symptoms of IgAV and IgAVN. This novel model, (partly) based on the work of Chiang et al. [54,55,63,64], includes the interaction between IgA and FcαRI, resulting in neutrophil activation and recruitment. Here, the first hit is the increased serum level of IgA1 AECA, possibly influenced by genetics or molecular mimicry (Fig. 4B). This is followed by

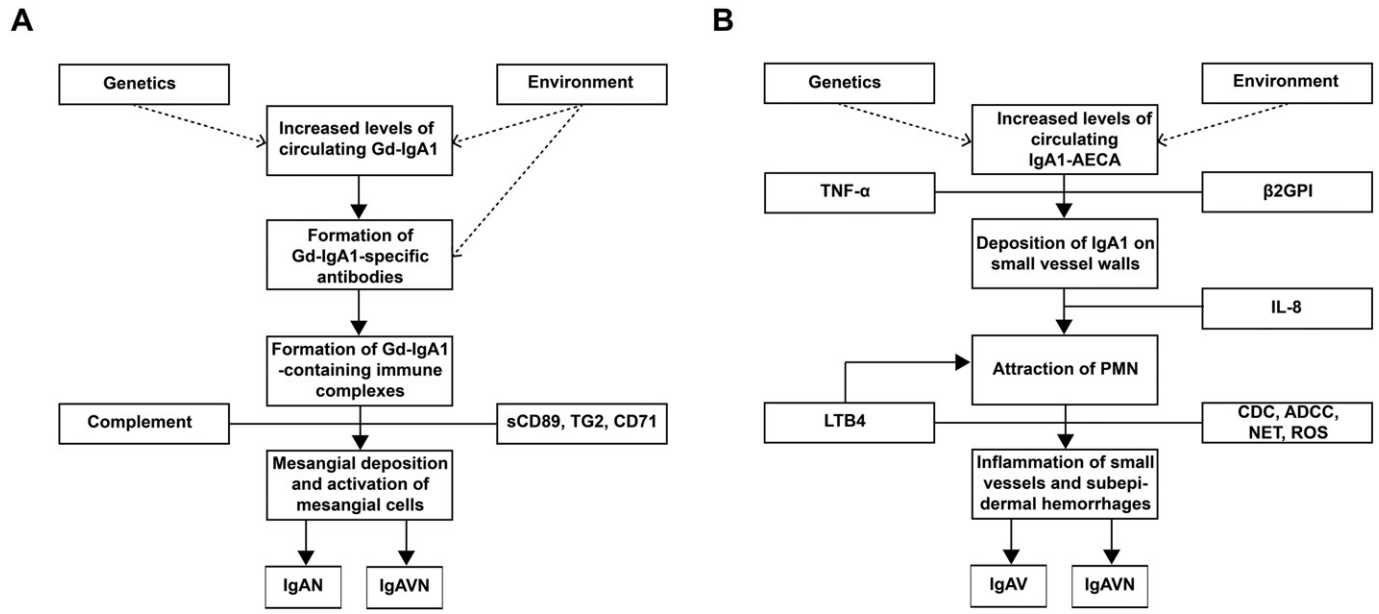

Fig. 4. Multi-hit pathogenesis model for (A) glomerulonephritis in IgAN and IgAVN and (B) vasculitis in IgAV and IgAVN.

the binding of IgA1 AECA to small vessels, which could include binding to β2GPI on endothelial cells. Third, the binding of AECA to human endothelial cells induces the production of IL-8, which is a potent chemoattractant for neutrophils. Lastly, the attracted neutrophils become activated by the interaction between IgA1 and FcαRI. Processes such as ADCC, CDC, NETosis and ROS production cause damage of vascular endothelial cells. Furthermore, IgA-activated neutrophils release LTB4, thereby attracting and activating other neutrophils in a positive feedback loop. Additionally, neutrophils release TNF-α, which is thought to further activate endothelial cells and induces endothelial cells to expose antigens which are normally hidden. AECA antibodies recognizing these antigens can subsequently bind to endothelial antigens. The activation of neutrophils ultimately leads to inflammation and vascular hemorrhaging as observed in IgAV and IgAVN.

7. Open questions and future research

Many open questions remain to be answered to fully understand IgA vasculitis (Table 2). Several factors complicate research into IgA vasculitis. First, since it is generally a self-limiting disease, minimal funding is devoted to unravel the underlying pathomechanisms. Second, it is difficult to obtain patient material in large sample sizes, since patients are often not hospitalized and disease course is usually benign. Third, since the classification of IgA vasculitis includes renal symptoms, data on IgAV patients often involves IgAVN patients as well. It is important to make a distinction between IgAV with and without glomerulonephritis to understand the differences in etiology between systemic and renal symptoms. Fourth, although multiple animal models for IgA nephropathy exist [36], literature on IgAV animal models is scarce. Rat and rabbit models developed for IgA vasculitis are induced by injecting the antigen ovalbumin and thereby inducing an allergic reaction [89–91]. It is unknown if these models are representative to study the pathomechanisms of IgAV. Additionally, most experimental animal species do not express FcαRI, which omits the effects of neutrophil activation via FcαRI. Therefore, model systems including humanized FcαRI are highly desired and necessary to fully understand pathogenesis of IgAV.

Table 2
Open questions regarding the pathogenesis of IgAV.

What is the form and origin of IgA1 in IgAV?
Are there immune complexes present in IgAV?
Is IgA1 in IgAV galactose-deficient?
To which antigen is IgA1 directed?
Do AECAs play a role in IgAV?
Why do some IgAV patients develop IgAVN?
Are IgAV, IgAVN and IgAN entities of the same disease?
Which role does complement play in etiology?
Does a genetic mutation or infectious agent trigger disease?
Are there differences in pathogenesis between pediatric and adult IgAV patients?

8. Conclusion

It has been hypothesized that IgAV, IgAVN and IgAN are all entities of the same disease. The two multi-hit hypotheses proposed here suggest that renal and systemic symptoms during IgAV, IgAVN and IgAN may have different origins (Fig. 4). IgAN is marked by the presence of Gd-IgA1, resulting in the formation of immune complexes, whereas IgA1 possibly recognizes endothelial cell antigens in IgAV. IgAVN could be viewed as a dual disease, in which both components of IgAV and IgAN are interwoven. Other factors, such as genetics, infection and complement also play a role in pathogenesis. Based on previous observations regarding the pathogenic role of the IgA Fc receptor FcαRI in LABD and RA, we anticipate that FcαRI plays an important role in etiology of IgA vasculitis by inducing neutrophil migration and activation. The unraveling of the exact pathomechanisms of IgAV will provide directions for prevention of disease, identification of biomarkers and future therapeutics.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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